71. (New) The method of Claim 62 wherein the compound is further characterized by having a functional activity at the human MC-2R and MC-3R with an EC_{50} greater than 1200 nM and a functional activity at the human MC-5R with an EC_{50} greater than 520 nM.

72. (New) A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 10-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

73. (New) The method of Claim 72 wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 100-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

74. (New) A method for the oral treatment of erectile dysfunction in a male subject which comprises the oral administration to the subject in need thereof a therapeutically effective amount of a compound which is an agonist of the human MC-4R.

75. (New) The method of Claim 74 wherein the compound is a selective agonist of the human MC-4R.

REMARKS

The Office Action dated March 11, 2002, has been carefully considered. The Applicants respectfully request reconsideration of the application in view of the following amendment, arguments, and remarks. The claims have been renumbered under Rule 1.126 to number from 1-38. Claims 1-38 have now been cancelled. New Claims 39-75 have been added directed to specific aspects of the claimed invention. The newly added claims are fully supported by the Applicants' specification and do not introduce new matter into the application. The newly presented claims recite methods of treating **male erectile dysfunction** with selective MC-4R agonists.

Claims 1-38 stand rejected under 35 USC 112, first paragraph, for lack of enablement, for the indicated reasons.

The Examiner has rejected the claims on the basis that the Applicants' specification does not enable the ordinary artisan how to choose a compound other than patented in the parent case, namely a substituted isoquinoline, for use as melanocortin-4 receptor (MC-4R) agonist to treat sexual dysfunction. The Applicants have cancelled the originally filed claims and have presented new claims reciting methods of treating male erectile dysfunction (MED) with selective MC-4R agonists. The Applicants respectfully disagree since their specification provides sufficient direction and guidance to enable the skilled artisan how to identify without undue experimentation selective MC-4R agonists as well as how to use them to treat MED.

The invention of Claims 39-75 is a method of treating MED with a compound that is a selective agonist of MC-4R as defined by the scope of the claims. The "critical reaction parameter" is selective activation of MC-4R. The present application clearly sets out for the skilled artisan how to identify compounds which **bind selectively** to MC-4R and which also function as **agonists** of MC-4R according to the scope of Claims 39-75 and then proceeds to describe how to evaluate their therapeutic properties in several *in vivo* models of MED. The methods to be used to identify selective binders of MC-4R are given on page 35 of the specification which details the assays that measure binding affinities to five melanocortin receptor subtypes. Next the methods needed to determine whether the selective binders of MC-4R also function as selective agonists of MC-4R are provided by a description of the functional assays on page 37 of the specification. These functional assays discriminate MC-4R agonists from antagonists. By a selective MC-4R agonist is meant a compound that binds to MC-4R and initiates a pharmacological response characteristic of only that receptor, that is, a compound that activates MC-4R and not the other four MC-R's. Finally, methods to use MC-4R-selective agonists to treat MED are provided on pages 38-39 of the specification which describe the rat *ex copula* model. Thus, how to identify and how to use compounds within the scope of Claims 39-75 are clearly set out in Applicants' specification. The identity of such compounds is not limited to, but is merely exemplified by, the isoquinoline compounds of the parent application. Since the Applicants' specification enables the "critical or essential method parameters which are necessary to the practice of the invention," no undue experimentation is required other than carrying out what is taught in the

specification. Example 84 constitutes a working example which clearly illustrates the operability of the present invention. The compound disclosed in Example 84 is representative of compounds that are selective agonists of human MC-4R within the scope of the claims which induce penile erections in the rat when administered either by the oral or parenteral route. The Applicants are willing to provide extrinsic evidence in the form of additional compounds which have been identified using the teachings found in the specification of the instant application.

Once a compound having the receptor binding and functional properties within the parameters of Claims 39-75 is identified, then the preparation of a pharmaceutical composition for systemic administration, as well as determining an appropriate dose and the route of administration, can be accomplished following the methods described in the instant application or modifications thereof which are known to one of ordinary skill in the pharmaceutical arts. Although some experimentation may be necessary, the pharmaceutical arts typically engage in such activity in the drug discovery process. The test of enablement is not whether any experimentation is necessary, but whether such necessary experimentation is undue (quoting from MPEP 2164.01). Moreover, the applicant need not demonstrate that the invention is completely safe (quoting from MPEP 2164.01(c)). Thus, the Applicants submit that one reasonably skilled in the art could make/use the present invention from the disclosures in the instant application coupled with information known in the art without undue experimentation.

Therefore, the Applicants submit that Claims 38-75 are fully enabled by the specification, and they therefore respectfully request that the section 112, first paragraph, rejection be withdrawn.

Claims 1-38 stand rejected under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over Girten (US Pat# 6,284,735), Nargund (US Pat# 6,294,534), Cone (US Pat# 5,837,521 and # 6,100,048) and Basu (US Pat # 6,127,381).

The instant application is a divisional application of Serial No. 09/585,111, filed June 1, 2000, which claims priority to provisional applications Serial No. 60/137,477, filed June 4, 1999, and 60/169,209, filed December 2, 1999. The earliest priority date of December 2, 1999, for the invention as presently claimed is earlier in time than the Sept. 4, 2001 issue date of

the Girten patent (US 6,284,735); the Sept. 25, 2001 issue date of the Nargund patent (US 6,294,534); the Aug. 8, 2000 issue date of the Cone patent (US 6,100,048); and the Oct. 3, 2000, issue date of the Basu patent (US 6,127,381).

The second Cone patent (US 5,837,521) discloses the cloning, expression, and functional characterization of the MC3 receptor. The present invention claims methods of treating male erectile dysfunction (MED) with selective agonists of the MC4 receptor over the MC3 receptor. Cone neither teaches nor suggests the use of selective MC4 agonists to treat MED. Thus, the claimed invention in the instant application is clearly distinguished from the disclosure in the second Cone patent (US 5,837,521).

Therefore, the Applicants respectfully request the withdrawal of the 102(b) or, in the alternative, the 102(b)/103 rejection over the Girten, Nargund, Cone, and Basu patents.

The Applicants believe that all of the objections and rejections have been overcome by argument, and therefore earnestly solicit an early allowance of the claims remaining under consideration.

Respectfully submitted,

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